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Pancreatic enzyme replacement therapy for young cystic fibrosis patients

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Abstract

Maldigestion in cystic fibrosis (CF) affects approximately 90% of patients. As soon as pancreatic insufficiency is identified, enzyme supplementation is prescribed even with breast fed infants. A pancreatic enzyme preparation developed particularly for infants, Creon® for children (CfC), contains smaller granules to be administered with a dosing spoon (5000 lipase units per scoop).

Patients and methods: In a prospective, randomised, multi-centre study, 40 infants and toddlers received both CfC and Creon® 10000 (C10) for two weeks each in a cross-over design. Dosing of pancreatic enzymes was continued as applied before the study. The primary endpoint was the parents' treatment preference. Secondary endpoints included coefficient of fat absorption (CFA), clinical symptoms and safety parameters.

Results: 20 parents (51%) from the $N=39$ intent to treat sample preferred CfC, 9 (23%) preferred C10, and 10 (26%) had no preference The applied doses led to a mean CFA with similar results for both treatments (77.8% vs. 78.7%). Gastrointestinal symptoms were reported on a number of study days, and some children had abnormal results for laboratory parameters of malabsorption. Safety and tolerability of the preparations were good and all these parameters were comparable for both treatments.

Conclusion: Those parents who had a preference favoured CfC over C10. Both enzyme preparations improved malabsorption to a similar degree, although the applied dosages could have been too low in some children reflected in a suboptimal CFA. These data support the use of CfC for young patients with cystic fibrosis improving the daily care of this cohort detected mainly now through neonatal screening programmes.

Keywords: Cystic fibrosis; Pancreatic insufficiency; Pancreatic enzyme replacement therapy; Coefficient of fat absorption; Neonatal screening

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1. Introduction

Cystic fibrosis (CF) is an autosomal recessive disease with a wide spectrum of clinical manifestations. The most frequent genetic defect in Europe, the F508del mutation, is almost invariably associated with pancreatic insufficiency (PI) [1]. Most affected children are identified on clinical symptoms during the first year of life, and pancreatic enzyme replacement therapy (PERT) is initiated immediately after the diagnosis of PI has been made [2,3] to allow an adequate growth. Implementation of CF neonatal screening programmes is increasing in Europe [4,5]; it allows very early diagnosis around one month of age.

Up to the mid 1980s, a fat-reduced diet was recommended but the development of acid-resistant microsphere preparations improved dramatically the stool fat loss in most patients [6,7] even with high energy diets without any dietary restrictions.

For infants, experts recommend lipase doses of 400 to 800 units per gram ingested fat [2,7] (one quarter to one half of a Creon® 10000 capsule (C10) per 120 ml feed of breast milk or formula). For parents of young infants, it remains difficult to administer such small doses. Creon® for children (CfC) was particularly developed for those who require small amounts of pancreatin or are unable to swallow capsules. Thus the preparation is provided as a bulk of minimicrospheres in a glass container, with a small spoon containing 5000 lipase units per scoop. This device facilitates more exact dosing of lower lipase units in small children.

The scientific literature contains very few data on objective measurements of malabsorption in infants with CF or on the efficacy and safety of enzyme preparations in this young age group [8–10].

The present trial was primarily designed to assess whether parents of infants prefer CfC over C10 on a lipase per lipase basis and to determine the efficacy of the preparations on clinical symptoms and laboratory measurements of malabsorption.

2. Patients and methods

2.1. Study design

This was a multi-centre, open, randomised, cross-over study in CF infants with PI to compare two pancreatic enzyme preparations, i.e. CfC and C10, with respect to their effect on malabsorption and to the parents' preference of one drug over the other (primary end point). The study was conducted at 13 sites in France between January and November 2004. Written informed consent was obtained from parents or legal guardians. The institutional review boards or ethical review committees had approved the study protocol.

The study consisted of a two-week run in period, after which children were randomised to treatment phase A to receive either CfC (one spoon with 100 mg granules containing lipase 5000 Ph. Eur. Units, amylase 3600 Ph. Eur. Units, protease 300 Ph. Eur. Units) or C10 (one capsule with 150 mg pancreatin labelled lipase 10000 Ph. Eur. Units, amylase 8000 Ph. Eur. Units, and protease 600 Ph. Eur. Units) for two weeks. The dose of lipase was kept constant compared to PERT before the study. After two weeks, a cross-over to treatment phase B was performed. Compliance with medication was determined from the number of dispensed and returned bottles or pots.

There were 4 study visits: 1) pre-study, 2) baseline and day 1 of treatment A, 3) end of treatment A, and 4) end of treatment B. No dosing advice was given but patients remained on their individual doses throughout the study. Doses were assessed in run-in period and in the treatment phase. To ensure that the lipid content of meals throughout the study was sufficient, the parents were requested to add 1 soup spoon of sunflower oil to lunch and dinner meals instead of their usual fat supplementation.

2.2. Patients

Patients were male or female between 6 and 36 months of age with a proven CF diagnosis (two positive sweat tests or mutation analysis). PI had been diagnosed by faecal pancreatic elastase-1 concentrations (74%), stool fat excretion (3%), and a combination of these and other tests (faecal chymotrypsin, PABA test). Exclusion criteria were meconium ileus or other conditions that had led to intestinal resection, severe concomitant diseases of other organ systems, any allergy to pancreatin or other drugs, or suspected non-compliance of subject or family.

2.3. Outcome measurements

The primary endpoint was the parents' preference of study medication at Visit 4, assessed by answering the question: "Which treatment did you prefer?" with one of the possible answers 1) Treatment (medication) 1 was better than Treatment (medication) 2, 2) Treatment 2 was better than Treatment 1, or 3) no difference between Treatment 1 and Treatment 2. In addition, parents were asked to give the reason for their preference (practicability, symptomatology, adverse event).

Secondary endpoints considered clinical symptoms and objective measurements of malabsorption. Stools samples were collected from day 12 to day 15 and from day 26 to 29, fat excretion was determined from each 3-day stool collection [11–13] at a central laboratory in Paris. Clinical symptoms related to malabsorption were recorded on each day of the study on diary cards with scales for stool frequency, stool consistency, flatulence, and abdominal pain. Dietary questionnaires were filled in from days 12 to 15 and from days 26 to 29. Fat as well as energy intakes were calculated from the diaries in order to calculate the coefficient of fat absorption (CFA) [13].

A dietician checked the accuracy of documented foods and quantities, then data were entered into the database Nutrilog Pro (Version 1.16, Nutrilog SAS, Ciqual, France 2001; Tables J.P. Blanc — Aliments de marque 2004).

2.4. Statistical analyses

The primary efficacy analysis was based on the ITT sample using Prescott's test [14] which takes into account the

possibility of a period effect. It was assumed that no carryover effect occurred.

The secondary efficacy variables were summarised descriptively, both by treatment and by treatment sequence and period. To assess the treatment effect, within-subject differences of treatment phase B minus phase A were compared between the sequences by exploratory tests (Wilcoxon–Mann–Whitney test). This accounts for possible period effects, and no carryover effect was assumed.

Safety analysis used the safety sample which consisted of all children who received at least one dose of study medication.

2.5. Determination of sample size

The following assumptions were made: 1) 20% of the parents have no preference, 2) 60% prefer CfC, and 3) 20% prefer C10. While applying Prescott's test with a level of significance of £0.05 (two-sided) and using a *t*-test approximation, one would need 17 subjects per sequence to achieve a statistical power of 80%. Since the exact test is slightly more conservative than the approximation, 18 subjects per sequence should complete both periods. To account for approximately 10% dropouts, 20 subjects per sequence were planned to be randomizedrandomised.

2.6. Safety analyses

Adverse experiences were monitored and height, weight, and vital signs were measured at each visit. A full physical examination was conducted at visits 1 and 4.

3. Results

3.1. Patients

Forty infants participated in the study. 19 were randomised to receive CfC and 21 to receive C10 during treatment phase A. One subject was withdrawn due to adverse events during the first treatment period, so that only 39 subjects were treated with C10. With the exception of the withdrawn subject who missed the last visit, all visits were attended. The intent-to-treat (ITT) sample consisted of 39. Girls represented 56.4%. The age range was 6 to 36 months with a mean of 19.2 months.

Before the study, 34 children (87%) had used C10 as PERT, 3 had used Creon® 25000, and 4 Creon® 5000. The mean (SD) intake of lipase during the run-in period was 4488 (3039) lipase units per kilogram and day (Table 1).

Table 1
Mean (SD) patient demographic features and baseline characteristics

	ITT population $N=39$
Age (months)	19.2 (9.5)
Gender (boys:girls)	17:22
Weight (kg)	10.1 (2.2)
Height (cm)	79 (0.9)
Lipase intake from PERT (units/kg/day)	4488 (3039)

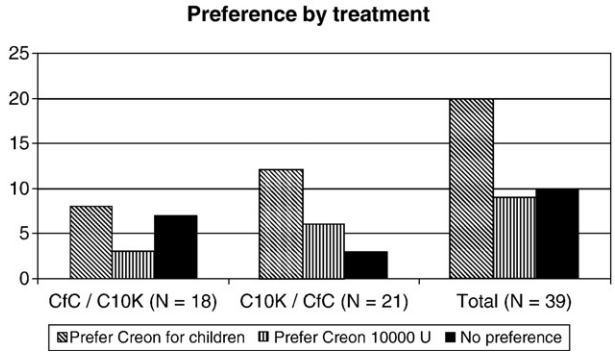

Fig. 1. Parents' preference of enzyme preparation. Parents' preference per treatment period for the two enzyme preparations CfC and C10.

3.2. Primary end point: Parents' preference of formulation

75% of parents had a preference for one treatment over the other: 51% preferred CfC, and 23% preferred C10. Parents preferred CfC for practicability reasons (13 subjects) and/or because their child had fewer symptoms (8 subjects). C10 was preferred because children had less gastrointestinal symptoms (4 subjects), because of practicability (3 subjects) or adverse event (1 subject, bronchial infection). Four parents gave no explanation and 2 mentioned 2 different reasons why they preferred a certain enzyme preparation.

The remaining 10 parents (26%) liked either enzyme preparation. (Fig. 1). Prescott's test for the comparison of treatments gave $p=0.066$ which did not reach statistical significance.

3.3. Secondary end points

3.3.1. Symptom diaries

On each study day, parents recorded symptoms of malabsorption in the subject's diary. The mean (SD) number of stools per day was 2.4 (1.1) with CfC and 2.3 (1.0) during C10 therapy. On the majority of days, stool consistency were either formed/normal (mean: 47.8% of days with CfC and 42.6% of days with C10, respectively) or soft (41.4% vs. 41.1%). Hard or watery stools were infrequent. Flatulence was a frequent event, occurring in a mild form on 23.1% of days during CfC and on 34.9% of days during C10 treatment, and moderate flatulence was observed on 9.0% and 7.3% of days, respectively. Children were free from abdominal pain on 91% of days during either treatment phase, and the percentage of days with mild or moderate abdominal pain was 9% in both groups.

Overall, there were no clinically relevant differences between treatments.

3.4. Calorie intake and stool fat analysis

Mean daily energy intake was 1100 kcal/day for a mean body weight of 10.1 kg. Fat intake was about 40 g/day (Table 2), with comparable mean daily lipase intakes during the CfC and C10 phases (3969 vs. 4310 U/kg/day). The mean faecal fat excretion was higher than desired (9.2 and 8.3 g per day during

Table 2
Secondary efficacy parameters: Mean (SD) dietary intake and malabsorption measurements

	Creon® for children ($n=39$)	Creon® 10,000 ($n=39$)	p value
Energy intake [kcal/day]	1105 (258)	1118 (304)	0.351
Fat intake [g/day]	42.8 (15.1)	41.9 (13.7)	0.727
Faecal fat [g/day]	9.2 (5.4)	8.3 (5)	0.119
Coefficient of fat absorption, CFA [%]	77.7 (13.1)	78.7 (14.0)	0.351
Faecal energy content [kcal/day]	138 (73.9)	135 (75.4)	0.419
Stool weight [g/day]	88.2 (45.3)	87.3 (49.5)	0.485

CfC and C10, respectively). The mean CFA was 77.8% and 78.7% during CfC and C10 treatment phases with some interindividual ranges. No differences between the two enzyme preparations were observed for all variables examined.

3.5. Safety

Determination of body weight, temperature, and pulse rate showed no relevant differences between the two medications, and the proportion of patients with adverse experiences was comparable between groups. No loss of body weight was observed with either treatment. In total, 17 subjects in each treatment group showed adverse events, mainly upper respiratory tract infections and gastrointestinal disorders. Adverse events reported for more than 2 subjects for any treatment was cough, toothache and nasopharyngitis as well as bronchitis. In total, three patients in the CfC group experienced related treatment emergent adverse events judged by the investigator (abdominal pain, constipation, vomiting) one patient in the C10 group (severe dermatitis diaper). Two serious adverse events (SAEs) were observed; both considered unrelated to study medication: a bronchial obstruction and acute otitis during C10 treatment, and *Pseudomonas aeruginosa* colonisation while receiving CfC. A toddler was prematurely withdrawn after six days of CfC, he experienced moderate abdominal pain and diarrhoea (possibly related to study medication, described above) and vomiting (unlikely related to study medication).

4. Discussion

Maldigestion due to PI is a characteristic feature of CF and the majority of patients therefore require PERT [15] CfC was developed particularly for infants and young children. A calibrated spoon allows take out of 5.000 units of lipase per dose out of a glass bottle containing pancreatin minimicrospheres.

The present study was primarily designed to evaluate how parents assess the handling of the new preparation, CfC, in comparison to the conventional C10 capsules, but also to assess efficacy and safety in comparison to established therapy. Due to the cross-over design of the trial, each parent tested both preparations. More parents (51%) preferred CfC over the conventional enzyme capsules (23%). However, more parents (26%) as anticipated did not express any preference thus the result did not reach statistical significance ($p=0.066$).

For the average study participant with a body weight of 10 kg, a daily lipase dose of 40,000 units would translate into 4 capsules of C10 or 8 spoons of CfC to be administered throughout 4 to 5 meals per day. Over half of the parents found it easier to take out spoons of CfC from the granule container rather than opening a capsule of C10. In infants it allows a better handling of smaller enzyme doses, particularly with the high numbers of feeding per day.

In addition to the primary objective of the trial, the results provide important insights into the situation of PERT in infants with CF. To our knowledge, this is the first original article describing the extent of malabsorption as well as energy and fat intakes in such a young patient population, being 3 years as the minimal age of participants in other studies [8–10]. Malabsorption measurements in the present study suggest that many infants had received suboptimal enzyme doses. During the conduct of our trial, the dose of PERT had been kept constant in each child and was the same as before the study. Mean lipase doses were about 3969 and 4310 units per kg body weight and day in the CfC and C10 phases, respectively. According to current European [2] and North American [16] recommendations, upper limits for PERT are 10,000 units of lipase/kg/day. Not surprisingly, the consequence of the relatively low pancreatin doses was a substantial faecal loss of energy with a mean fat excretion of 9 g per day during CfC (normal: <4.3 g/d in infants and <3.1 g/d in children) [7]. These results underline that faecal fat excretion measurements may be important tools if clinicians wish to assess the appropriate PERT supplementation in these young children. Our study demonstrated an insufficient fat assimilation with the recommended PERT dosage, emphasizing the need for further studies aimed at reviewing the present guidelines for PERT in infants.

The mean observed CFA of 79% in our patients was lower than desired, although at the individual levels some patients had normal fat absorption up to 98%. In randomised controlled PERT studies, untreated CF patients on placebo had mean CFAs between 45% and 55%, while adequate enzyme replacement increased CFA to about 80% to 90% [7]. Some authors reported even higher CFAs with sufficient pancreatin doses [10,17]. Young children achieve sufficient growth and weight gain more easily when only small amounts of fat and energy are lost in the stool. Increases in weight were larger during treatment with an acid resistant enzyme preparation than after an uncoated pancreatin formulation [18]. The present study with 4 weeks duration demonstrated no loss of body weight with either treatment but was too short to evaluate body weight development for clinical relevance.

One of the aims of PERT is also to abolish unpleasant gastrointestinal symptoms [7]. The clinical end-points of our trial show some issues in well-being that might have been caused by malabsorption. Parents recorded flatulence on up to 43% of study days and mild or moderate abdominal pain on 9% of study days. One could speculate that after the occurrence of fibrosing colonopathy in the early 1990s, physicians might have been reluctant to prescribe larger enzyme doses. It may also be

that parents tended to underreport symptoms when asked during routine clinic visits, while the daily records as part of a clinical trial presented a more objective picture of abdominal pain and distension. Since the study physicians were experienced caregivers working at certified CF centres, we have no doubt that these results are representative for other young children with cystic fibrosis. From a clinicians' point of view, one of the drawbacks of our study was that no attempt was made to optimise the Creon® dose before randomisation. This would certainly have been necessary if the primary focus of the study had been the efficacy of pancreatin preparations for treating malabsorption.

In conclusion, the results of the present study suggest that parents of young CF children tend to prefer Creon® for children over Creon® 10000 capsules. A subgroup of parents liked either enzyme preparation, which is reassuring since older children will need enzymes capsules later in their lives.

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Ethics approval. This study was approved by the Comité Consultatif de protection des Personnes qui se pretent à la Recherche Biomédicale (CCPPRB) Paris, Bichat Claude Bernard, France on 13 October 2003 prior to the study being implemented. The study was conducted according to the ethical principles stated in the latest Declaration of Helsinki (1996 version), the applicable ICH guidelines for good clinical practice, and French regulatory requirements.

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